FLUORINATED ANALOGUES OF THE IMIDAZOLE INSECT GROWTH REGULATOR KK-42

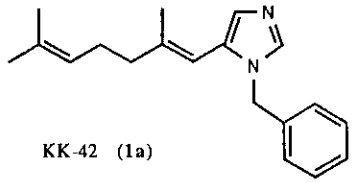
César Arbonés, Francisco J. Sánchez, Maria-Pilar Marco, Francisco Camps, and Angel Messeguer*
Department of Biological Organic Chemistry, C.I.D. (C.S.I.C.)
J. Girona, 18. 08034 Barcelona, Spain

Abstract - The preparation of compounds **1b**, **1c** and **1e**, monofluoro and trifluoromethyl analogues of the imidazole KK-42 (**1a**) is reported. The synthetic sequence involves the formation of an imine between the appropriate fluoro aldehyde and benzylamine, followed by condensation with tosylmethyl isocyanide (TosMIC) in basic media. Each step has been thoroughly studied and the whole procedure has been optimized for the case of model imidazole **1a**. It has been observed that when possible, the imine formation proceeds with a concomitant Z/E isomerization on the olefin moiety of the α,β-unsaturated system. Finally, data on the biological activity of the title compounds as ecdysone antagonists are also presented.

INTRODUCTION

The development of insect hormone antagonists is a subject of continuous interest for insect pest control. Within the context of either insect juvenile hormones or moulting hormones (ecdysones), several approaches have been carried out to obtain new compounds which could exhibit an activity as antagonists of these hormones.[1,2] One of the strategies more widely used for this purpose has been the design of biosynthesis inhibitors; in particular, since cytochrome P-450 monooxigenases are involved in different steps of the biosynthesis of both hormones, potential specific inhibitors of these enzymatic systems have been subject of active research. However, if the activity of a given antagonist is not specific, a compound designed as insect juvenile hormone inhibitor could also present an antiecdysone action. It seems that this is the case of imidazole KK-42 (**1a**). This compound was developed by E. Kuwano et al.,[3] being the optimized molecule from a series of 1,4- and 1,5-disubstituted imidazoles tested for

antijuvenile hormone activity,[4-6] particularly on the silkworm Bombyx mori. Nevertheless, recent findings suggest that this compound exhibits also activity as ecdysone antagonist.[7]



KK-42 (1a)

In the present paper we report an optimized preparation of model compound **1a** and the synthesis of monofluoro and trifluoromethyl analogues **1b**, **1c** and **1e**. According to our experience on the synthesis of fluorinated terpene synthons containing the fluorine atoms in the vicinity of olefin moieties,[8-10] we deemed that replacement of the (E)-2,6-dimethyl-1,5-heptadienyl substituent of imidazole KK-42 by fluoro terpene moieties could induce changes on the lipophilic character of the compound and additional resistance to metabolic degradation. In all cases, we have used the synthetic sequence described by Kuwano et al.,[3] although it has been improved, particularly for the reaction which leads to the formation of the intermediate imines **3**. In addition, biological activity assays for compounds **1a**, **1b** and **1e** as ecdysone antagonists have also been performed.

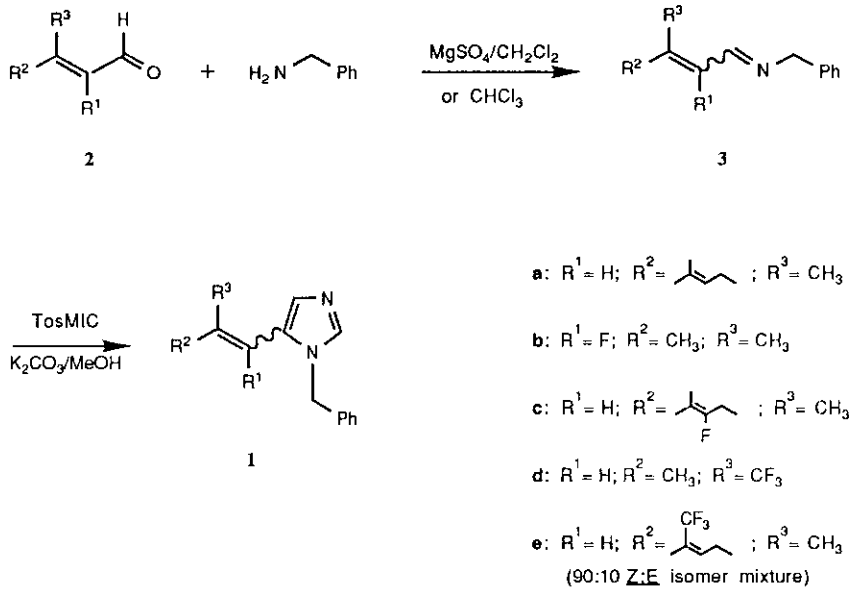
RESULTS AND DISCUSSION

Synthesis of model imidazole **1a**.

The procedure reported by Kuwano et al. for the synthesis of **1a** is depicted in Scheme 1. Thus, condensation of geranial with benzylamine in the presence of magnesium sulphate afforded the intermediate imine **3**, which was allowed to react with tosylmethyl isocyanide (TosMIC)[11] to give a 2:1 mixture of imidazole KK-42 and its corresponding Z-isomer in 35% overall yield. Since the sequence appeared to be convenient for the preparation of the designed fluorinated analogues, we decided to reinvestigate its scope with the aim of improving the yields and minimizing the observed isomerization process.

In fact, an almost quantitative conversion was observed when geranial (**2a**) reacted with benzylamine under the above conditions. However, the ^{1}H nmr of the crude reaction mixture (triplets at δ= 8.32 and 8.26 and singlets at 1.93 and 1.88) showed the presence of two imines in a 7:3 isomeric ratio, which were identified as the E:Z **3a** isomers, respectively. The lack of bibliography on the

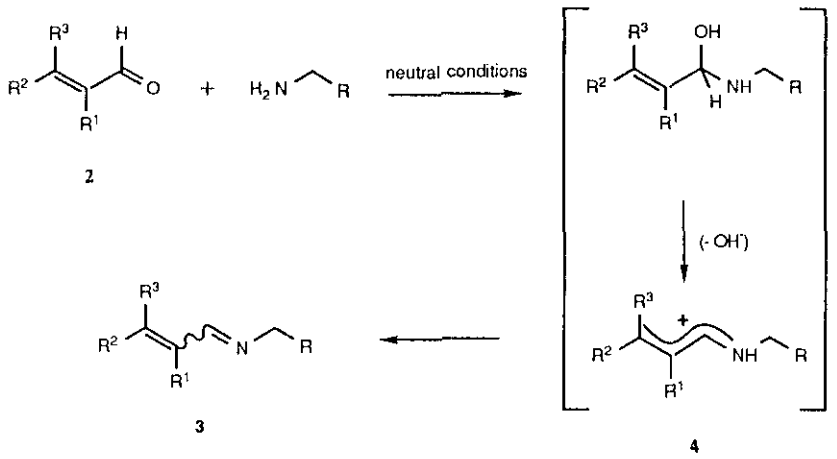
reaction of amines with α,β-unsaturated aldehydes led us to perform several assays to rationalize the observed isomerization.



Scheme 1

Although the unstability of these imines precluded its separation by chromatographic means, treatments with 0.1 N HCl were needed to revert to the precursor aldehydes geranial and neral, which were also formed in a 7:3 isomeric ratio, respectively. In addition, it was confirmed that pure geranial (**2a**) did not isomerize under the above acid conditions. On the other hand, reaction of benzylamine with neral afforded the same imine mixture, which indicated that the observed isomerization was independent on the aldehyde configuration geometry. Since substitution of triethylamine (an amine that cannot condense to give an imine) for benzylamine did not induce isomerization on the precursor aldehydes and the use of cyclohexylamine also led to a 7:3 isomeric ratio of the corresponding imines, our conclusion was that the observed isomerization occurs during the condensation between the aldehyde and the primary amine. Thus, it is plausible that an intermediate such as **4** (Scheme 2) could undergo allylic rearrangement under the reaction conditions giving rise to a Z : E mixture, which would be converted into the final imines **3** with an isomeric ratio derived from the respective thermodynamic stabilities. Incidentally, when some of the above assays were carried out in deuteriochloroform for monitoring the reaction course by ^{1}H nmr, it was observed that the condensation took place faster (15 min) and the working-up

of the crude reaction mixture was also much simpler in comparison with the magnesium sulphate/dichloromethane conditions currently used (3 h). After different attempts, it was found that the use of not newly distilled chloroform (which ensured a slight acid medium) gave the best results for these class of condensations.



2 3 4

Scheme 2

Finally, reaction of the isomeric mixture of imines with TosMIC in the presence of potassium carbonate in methanol gave a 7:3 mixture of imidazole **1a** and its corresponding Z isomer, which was separated by column chromatography on silica gel. It is worth to point out that a considerable improvement of the chromatographic separation was achieved by saturating the eluent mixtures with ammonium hydroxide (28% aqueous solution). By this procedure, the pair of imidazoles were isolated with a 70% overall yield from starting aldehyde **2a**.

Synthesis of fluoro analogues.

The different fluoro aldehydes needed for the preparation of imidazoles **1b-1e** were obtained from precursors already available in our laboratory.[8,9]

Thus, 2-fluoro-3-methylbut-2-enal (**2b**) was prepared from isobutyraldehyde according to the procedure reported by Schlosser and coworkers[12] with minor modifications. Specifically, hydrolytic opening of the chlorofluorocyclopropane precursor of **2b** was carried out with a 1:1 dioxane:water mixture (3 h at 70 °C). This treatment was milder than that previously reported[12] and afforded the aldehyde in 90% yield.

The fluoro aldehyde **2c** was obtained from the corresponding methyl ester[8] by reduction with lithium aluminium hydride followed by oxidation with

manganese dioxide (72% overall yield). A similar procedure was used for the preparation of trifluoromethylbutenal **2d** from its corresponding methyl ester,[10] although in this case the high volatility of the aldehyde advised the use of pyridinium dichromate as oxidation reagent to minimize losses during the work-up of the crude reaction mixture (66% overall yield). Finally, trifluoromethyl aldehyde **2e** was prepared from the corresponding tetrahydropyranyl protected alcohol[9] by hydrolysis and subsequent oxidation with manganese dioxide, in 77% overall yield.

Furthermore, reaction of fluoro aldehydes **2b-2e** with benzylamine led to the formation of the corresponding imines **3** in yields comparable with those obtained for imine **3a**. Again, a 7:3 isomeric mixture of imines was obtained for **3c**, **3d** and **3e**, which was E : Z, respectively, for the first and the third, and Z : E for the second. These intermediates could not be isolated and they were identified by spectroscopic means.

The final conversion of the imines into the corresponding imidazoles was tried by using the procedure described above for the case of model compound **2a**, and we were succesful for the case of imines **2c** and **2e**, which gave good yields of fluoroimidazoles **1c** and **1e**, respectively. Obviously, these compounds were also obtained as a 7:3 E:Z isomeric mixture. These mixtures could also be separated by column chromatography on silica gel, saturating the eluent mixture with ammonium hydroxide (28% aqueous solution) to improve isomer separation.

Conversely, the reaction of imines **3b** and **3d** with TosMIC reagent was troublesome. Thus, all attempts carried out to obtain the trifluoromethylimidazole **1d** were unsuccesful, probably due to the electron withdrawing effect of the CF_3 group, which caused a change in the charge distribution along the α,β-unsaturated system of the imine. This alteration could be particularly important on the iminic carbon atom, which is supposed to be the target for the initial attack of the TosMIC generated carbanion.[11]

The case of imine **3b** was slightly different. This intermediate appeared to be also inactivated by the effect of the fluoro substituent, since reaction with TosMIC was much slower than with former imines **3a**, **3c** or **3e**, and consequently, yields were also reduced due to the unstability of the isocyanide under the reaction conditions.[11] However, as we have previously shown, the deactivation induced by a fluoro substituent on an olefin moiety is not very strong;[8] thus, if self decomposition of TosMIC could be minimized, there would be possible to prolonge reaction times and then achieve the imidazole formation. After several attempts, substitution of diisopropylamine for

potassium carbonate resulted in the stabilization of the reagent and imidazole **1b** could be obtained in 70% yield.

Biological Assays.

Imidazoles **1a**, **1c** and **1e**, only E isomers,[13] were assayed as potential ecdysone antagonists in pupae of Tenebrio molitor. Accordingly, compounds (10 μg) were injected as hydrochlorides (1 μl of an aqueous solution at pH 6) into newly emerged pupae that had been anesthesized under ice for 20 min. Controls received the corresponding amount of solvent. After 4 days, hemolymph was obtained by cutting off the pupae legs. The extract (about 5 μl) was deproteinized by precipitation in methanol (200 μl) and centrifugation (5 min at 10000 g). The supernatant layer was evaporated with nitrogen stream and redisolved in phosphate buffer (0.1 M, pH=7.4). The levels of ecdysone-like compounds were determined by the enzyme immunoassay reported by Porcheron et al.[14] The results obtained are depicted in Table 1.

Table 1. Titers of ecdysone-like immunogens in Tenebrio molitor pupae treated with imidazole KK-42 and the fluoro analogues **1c** and **1e**.

Compound	ng ecdysone / ml hemolymph [a]	n
Control	4058 ± 320	13
1a	4244 ± 408	9
1c	2849 ± 355	8
1e	5787 ± 377	9

[a] Values determined using the enzyme immunoassay reported by Porcheron et al.[14] and are given as X ± S.E.M.

As shown, imidazole KK-42 (**1a**) did not deplete ecdysone titers, which suggests that this compound does not behave as ecdysone antagonist on T. molitor pupae. On the other hand, monofluoro analogue **1c** elicited a slight but significant inhibition (30% with respect to controls, $P < 0.05$). This inhibition, however, was lower than that exhibited by azadirachtin, a potent ecdysone antagonist previously assayed in our laboratory. Finally, it is worth of note the

stimulatory activity (40% with respect to controls, $P < 0.005$) elicited by the trifluoromethyl derivative **1e**. This activity could present a parallelism with the also unexpected stimulation elicited by methyl 12,12,12-trifluoro-methylfarnesoate, a compound with the same fluoroterpenoid moiety as of **1e**, that we found in the biosynthesis of insect juvenile hormone III by the corpora allata of Blattella germanica. In summary, these results, besides pointing out the different effects of fluoro substituents depending upon its position in respect to an olefin moiety, also raise an intriguing question about a hypothetical relationship between trifluoromethyl olefinic fragments and stimulation of insect hormones biosynthetic pathways. Work along this line is in progress in our laboratory.

EXPERIMENTAL

Melting points (uncorrected) were determined with a Koffler apparatus. Elemental analyses were obtained with a Carlo Erba Model 1106 instrument. Ir spectra were performed with a Perkin Elmer 399 B apparatus in CCl_4 solutions. ^1H and ^{19}F nmr spectra were recorded on a Bruker WP-80 SY spectrometer in $CDCl_3$ solutions. Chemical shifts are reported in ppm downfield from internal *TMS for ^1H and external 1% CF_3COOH in $CDCl_3$ for ^{19}F* . *The following* descriptions for the observed multiplicities are used: br = broad, d = doublet, q = quartet, s = singlet, t = triplet. Gc-ms analyses with electron impact were performed with a Hewlett-Packard Model 5995-C instrument, using a OV-101 glass capillary column (25 m). Ms analyses with electron impact were obtained with a VG TS-250 spectrometer. Microdistillations were carried out with a Buchi Kugelrohr Model GKR-50. Unless otherwise stated, organic extracts obtained from treatment of reaction crudes were dried over magnesium sulphate and solvent was removed by evaporation under vacuum.

N-(3,7-Dimethyl-2,6-octadienyliden)benzylamine (**3a**). Geranial (0.6 g, 2.9 mmol) was added to a solution of benzylamine (0.32 g, 3 mmol) in CH_2Cl_2 (8 ml), containing $MgSO_4$ (0.5 g). The mixture was stirred under reflux for 3 h (gc monitoring), cooled down and filtered. The residue obtained from solvent removal was identified by ^1H nmr as a 7:3 E:Z mixture of **3a** and its corresponding isomer, which could not be separated by chromatographic means. When the reaction was carried out in $CHCl_3$, using the same amount of *aldehyde and amine but without $MgSO_4$, gc monitoring revealed an almost* quantitative conversion after 15 min stirring at room temperature.

Ir (ν, cm^{-1}): 1645, 1610; ms (m/z): 241 (M^+), 198, 161, 150, 91.

E isomer. ^{1}H Nmr: 1.65 (s, 3H), 1.67 (s, 3H), 1.92 (d, 3H, J=1 Hz), 2.15 (m, 4H), 4.63 (br s, 2H), 5.10 (br t, 1H, J=7 Hz), 6.08 (br d, 1H, J=9 Hz), 7.28 (br s, 5H), 8.32 (dt, 1H, J_1=9, J_2=1 Hz).

Z isomer. ^{1}H Nmr :1.58 (s, 3H), 1.60 (s, 3H), 1.88 (d, 3H, J=1 Hz), 2.15 (m, 4H), 4.63 (br s, 2H), 5.10 (br t, 1H, J=6 Hz), 6.07 (br d, 1H, J=9 Hz), 7.28 (br s, 5H), 8.26 (dt, 1H, J_1=9, J_2=1.5 Hz).

When the reaction was carried out with pure neral (obtained from chromatography on silica gel of a geranial-neral mixture, eluting with 98:2 hexane:ether), analysis of crude reaction mixture by ^{1}H nmr after 3 h showed the presence of the same 7:3 isomeric mixture of imines.

N-(3,7-Dimethyl-2,6-octadienylidene)cyclohexylamine. Following the procedure described above for the case of benzylamine, geranial (0.030 g, 0.2 mmol) and cyclohexylamine (0.019 g, 0.2 mmol) were allowed to react. Conventional work-up of the crude reaction mixture gave a residue containing a 7:3 E:Z mixture of the corresponding imines (conversion over 95%).

Ir (ν, cm^{-1}) : 1645, 1610.

E isomer. ^{1}H Nmr :1.15-1.45 (br s, 11H), 1.67 (br s, 6H), 1.91 (d, 3H, J=1 Hz), 2.15 (m, 4H), 5.10 (br s, 1H), 6.06 (br d, 1H, J=9 Hz), 8.22 (dd, 1H, J_1=9, J_2=1 Hz).

Z isomer. ^{1}H Nmr :1.15-1.45 (br s, 11H), 1.60 (br s, 6H), 1.86 (d, 3H, J=1 Hz), 2.15 (m, 4H), 5.10 (br s, 1H), 6.06 (br d, 1H, J=9 Hz), 8.18 (dd, 1H, J_1=9, J_2=1 Hz).

1-Benzyl-5-(2,6-dimethyl-1,5-heptadienyl)imidazole. Following the general procedure described by Van Leusen et al.[11] TosMIC (0.62 g, 3.2 mmol) was added to a suspension of the isomeric mixture containing *imine* **3a** (0.70 g, 2.9 mmol), K_2CO_3 (1.5 g, 10.9 mmol) and MeOH (8 ml). The crude reaction mixture was stirred under reflux until gc monitoring showed the absence of starting imines (3 h), and filtered through celite, washing thoroughly with CH_2Cl_2. The residue obtained after solvent removal (a 7:3 E:Z isomeric mixture of the corresponding imidazoles) was purified by chromatography over silica gel, using a mixture of 2:1 hexane:AcOEt saturated with ammoniun hydroxide (28% aqueous solution), to give **1a** and its Z isomer in 70% overall yield from starting geranial.

1a: mp 62-64 °C (lit.[3] 62-64 °C); ir (ν, cm^{-1}) : 3060, 2960, 2910, 1480, 1450, 1440, 1370, 1350, 1270, 1230, 1115, 915; ^{1}H nmr : 1.61 (br s, 3H), 1.68 (br s, 3H), 1.83 (d, 3H, J=1 Hz), 1.95-2.40 (m, 4H), 4.96-5.20 (br s, 3H), 5.76 (s, 1H), 6.90-7.35 (br s, 6H), 7.46 (s, 1H); ms (m/z) : 280 (M^+), 211, 91.

Z isomer: mp 80-82 °C (lit.[3] 80-82 °C); ir (ν, cm^{-1}) : 3060, 2960, 2910,1480, 1450, 1350, 1270, 1220, 1110, 1030, 925; ^{1}H nmr : 1.54 (br s, 3H), 1.62 (br s,

3H), 1.81 (d, 3H, J=1 Hz), 2.10 (m, 4H), 5.00-5.10 (br s, 3H), 5.76 (s, 1H), 6.90-7.35 (br s, 6H), 7.45 (s, 1H); ms (m/z) : 280 (M^+), 211, 91.

2-Fluoro-3-methylbut-2-enal (**2b**). This compound was prepared according to the procedure reported by Schlosser and coworkers[12] with some modifications in the last step of the synthetic sequence. Specifically, intermediate 1-chloro-1-fluoro-2-ethoxy-3,3-dimethylcyclopropane (6 g, 36 mmol) was added to 50 ml of a 1:1 water:dioxane solution and the mixture was heated at 70 °C under N_2 until the reaction was completed (3 h, nmr monitoring). The crude reaction mixture was extracted with ether (3 x 25 ml) and the organic extracts were dried. After elimination of solvents by distillation, the residue was distilled under vacuum to give 3.30 g (bp 46 °C/50 torr, 90% yield) of **2b**.

2b[12]: Ir (ν, cm^{-1}): 1690; ^1H nmr: 1.94 (d, 3H, J=4 Hz), 2.13 (d, 3H, J=3 Hz), 9.70 (d, 1H, J=16 Hz).

(2E)-6-Fluorogeranial (**2c**). A solution of ethyl (2E)-6-fluorogeranate[8] (1.0 g, 5 mmol) in dry ether (2.5 ml) was added dropwise to a suspension of $LiAlH_4$ (0.19 g, 5 mmol) in the same solvent (2.5 ml) maintained at 0 °C and the mixture was stirred at the same temperature. When the reaction was completed (40 min, gc monitoring), conventional work-up of the crude reaction mixture gave the corresponding alcohol (0.77 g, 90%). Ir (ν, cm^{-1}) : 3600-3200 (br), 1710; ^1H nmr : 1.55-1.65 (m, 6H) , 1.75 (s, 3H), 2.00-2.60 (m, 4H), 4.15 (d, 2H, J=7 Hz), 5.42 (br t, 1H, J=7 Hz). Subsequently, active MnO_2 (10 g) was added to a solution of the fluoro alcohol (0.35 g, 2.0 mmol) in hexane (70 ml) and the mixture was vigorously stirred for 20 h at room temperature. The insoluble material was removed by filtration, washing thoroughly with ether and the filtrate was carefully evaporated under vacuum to give a residue containing the fluoroaldehyde **2c** (0.28 g, 80% yield).

2c: Ir (ν, cm^{-1}) : 1710, 1685; ^1H nmr : 1.56 (d, 3H, J=3 Hz), 1.64 (d, 3H, J=3 Hz), 2.18 (d, 3H, J=1.5 Hz), 2.35-2.70 (m, 4H), 5.89 (br d, 1H, J=8 Hz), 9.99 (d, 1H, J=8 Hz). Anal. Calcd for $C_{10}H_{15}FO$: C, 70.61; H, 8.81. Found: C, 70.45; H, 8.96.

(2Z)-3-Trifluoromethylbut-2-enal (**2d**). By using the same procedure described above, methyl (2Z)-trifluorobut-2-enoate[10] (2.25 g, 13.4 mmol) was reduced with $LiAlH_4$ (0.5 g, 13.4 mmol) in dry ether (10 ml). In this case, after conventional work-up of the crude reaction mixture, ether (20 ml) was carefully eliminated by distillation using a Vigreux column, to give a residue which contained the expected trifluoromethyl alcohol (1.27 g, 68% yield) identified by comparison with an authentic sample independently prepared.[10] Ir (ν, cm^{-1}) : 3600, 3600-3200 (br), 1620; ^1H nmr : 1.45 (br s, 1H), 1.88 (q, 3H, J=2 Hz), 4.20-4.50 (m, 2H), 6.20 (br t, 1H, J=7 Hz); ^{19}F nmr : 15.4 (q, J=2 Hz).

Subsequently, a solution of this alcohol (0.5 g, 3.6 mmol) in DMF (1.5 ml) was added to a solution of pyridinium dichromate (1.7 g) in the same solvent (2 ml), maintained at -10 °C.[15] After stirring for 5 h at this temperature, the crude reaction mixture was acidified with 0.5 N HCl (25 ml) and extracted with CH_2Cl_2. The joined organic extracts were dried and solvents were partially removed by distillation, leaving an enriched solution containing the expected aldehyde **2d**, which was identified by comparison with an authentic sample independently prepared[16] (75% yield estimated by ^1H nmr using methyl formate as internal standard). ^1H Nmr : 2.20 (q, 3H, J=1 Hz), 6.45 (br d, 1H, J=9 Hz), 10.15 (dd, 1H, J_1=9, J_2=2 Hz).

(2E,6Z)-8,8,8-Trifluorogeranial (**2e**). A solution of the tetrahydropyranyl ether of (2E, 6Z)-8,8,8-trifluorogeraniol[9] (2.0 g, 6.8 mmol, 6E: 6Z 5:95 isomeric ratio) in MeOH (50 ml) was treated with pyridinium *p*-toluenesulphonate (0.17 g, 0.7 mmol) and the mixture was heated at 40 °C until hydrolysis was completed (5 h, gc monitoring). Then the crude reaction mixture was poured into water (250 ml) and extracted with pentane (5 x 70 ml). The combined organic extracts were dried and the residue obtained after solvent removal was identified as the corresponding alcohol (1.27 g, 90% yield). Ir (ν, cm^{-1}) : 3600-3200 (br), 1645; ^1H nmr : 1.68 (s, 3H), 1.85 (q, 3H, J=2 Hz), 1.90-2.60 (m, 4H), 4.20 (d, 2H, J=7 Hz), 5.48 (t, 1H, J=7 Hz), 5.73 (t, 1H, J=7 Hz); ^{19}F nmr : 14.2 (6Z). Subsequently, a solution of this alcohol (0.40 g, 1.9 mmol) in hexane (70 ml) was treated with activated MnO_2 (10 g). After conventional work-up, pure aldehyde **2e** was isolated after chromatography on silica gel using a mixture 8:2 hexane:ether (0.34 g, 85%).

2e: Ir (ν, cm^{-1}) :1680; ^1H nmr : 1.85 (q, 3H, J=2 Hz), 2.20 (d, 3H, J=1.5 Hz), 2.30-2.70 (m, 4H), 5.73 (t, 1H, J=7 Hz), 5.90 (d, 1H, J=8 Hz), 10.00 (d, 1H, J=8 Hz); ^{19}F nmr : 14.0 (6Z). Anal. Calcd for $C_{10}H_{13}F_3O$: C, 58.28; H, 6.30. Found: C, 58.48; H, 6.66.

Preparation of imines **3b-3e**. These compounds were obtained using the general procedure described above for imine **3a**.

3b: from aldehyde **2b** (0.4 g, 3.9 mmol) and benzylamine (0.43 g, 4 mmol), 0.75 g (95 % yield) of imine were obtained. ^1H Nmr : 1.87 (s, 6H), 4.74 (br s, 2H), 7.30 (s, 5H), 8.14 (d, 1H, J=19 Hz).

3c: from aldehyde **2c** (0.30 g, 1.8 mmol) and benzylamine (0.20 g, 1.8 mmol), 0.43 g (94 % yield) of a 7:3 E : Z isomeric mixture of imines was obtained. ^1H Nmr: 1.50-1.60 (br s, 12H), 1.88 (d, 3H, J=1 Hz, Z isomer), 1.95 (d, 3H, J=1 Hz, E isomer), 2.30 (m, 4H), 2.55 (m, 4H), 4.65 (br s, 4H), 6.10 (d, 2H, J=9 Hz), 7.30 (s,

10H), 8.20 (dt, J_1=9, J_2=2 Hz, Z isomer), 8.35 (dt, 1H, J_1=9, J_2=2 Hz, E isomer); ms (m/z) : 259 (M^+), 239, 91.

3d: from aldehyde **2d** (0.35 g, 2.5 mmol) and benzylamine (0.27 g, 2.5 mmol), 0.52 g (90 % yield) of a 7:3 Z : E isomeric mixture of imines was obtained. ^{1}H Nmr: 2.05 (br s, 3H), 4.75 (br s, 2H), 6.75 (d, 1H, J=9 Hz), 7.30 (s, 5H), 8.35 (br d, 1H, J=9 Hz); ms (m/z) : 227 (M^+), 158, 91.

3e: from aldehyde **2e** (0.30 g, 1.5 mmol) and benzylamine (0.16 g, 1.5 mmol), 0.40 g (92 % yield) of a 7:3 E : Z isomeric mixture of imines was obtained. ^{1}H Nmr: 1.75-1.80 (m, 6H), 1.85 (br s, 6H), 2.30-2.40 (m, 8H), 4.63 (br s, 4H), 5.65 (br s, 2H), 6.06 (br d, 2H, J=9 Hz), 7.25 (s, 10H), 8.20 (dt, 1H, J_1=9, J_2=1.5 Hz, 2Z isomer), 8.25 (dt, 1H, J_1=9, J_2=1.5 Hz, 2E isomer); ms (m/z) : 295 (M^+), 204, 172.

Preparation of imidazoles **1b**, **1c** and **1e**. Fluoro compounds **1c** and **1e** were prepared and purified as described above for the model imidazole **1a**. In the case of **1b**, K_2CO_3 was replaced by diisopropylamine.

1b: from imine **3b** (0.10 g, 0.5 mmol), diisopropylamine (0.12 g, 1.2 mmol), TosMIC (0.11 g, 0.6 mmol) in MeOH (5 ml). The mixture was heated for 15 h under reflux and the imidazole was isolated (0.084 g, 70% yield) by column chromatography on silica gel using a mixture of 2:1 hexane:AcOEt saturated with ammoniun hydroxide (28% aqueous solution). mp : 101-103 °C; ir (ν, cm^{-1}) : 2980, 2930, 2850, 1540, 1495, 1450, 1380, 1355, 1230, 1110, 1075, 920; ^{1}H nmr : 1.52 (d, 3H, J=3 Hz), 1.75 (d, 3H, J=3 Hz), 5.09 (s, 2H), 7.10-7.50 (br s, 6H), 7.54 (s, 1H); ^{19}F nmr : -31.7; ms (m/z) : 230 (M^+), 139, 91. Anal. Calcd for $C_{14}H_{15}FN_2$: C, 73.04; H, 6.54; N, 12.17. Found: C, 73.02; H, 6.19; N, 12.13.

1c: from the corresponding imine mixture (0.40 g, 1.5 mmol), K_2CO_3 (0.80 g, 5.8 mmol), TosMIC (0.30 g, 1.5 mmol) in MeOH (8 ml), a 7:3 E : Z isomeric mixture of imidazoles (0.31 g, 68% yield) was obtained, which was separated by column chromatography on silica gel using a mixture of 2:1 hexane:AcOEt saturated with ammoniun hydroxide (28% aqueous solution). **1c**: mp 87-88 °C; ir (ν, cm^{-1}) : 3050, 3020, 2920, 2860, 1710, 1480, 1450, 1350, 1230, 1150, 1100, 1025, 915; ^{1}H nmr : 1.55-1.65 (m, 6H), 1.85 (s, 3H), 2.20-2.50 (m, 4H), 5.10 (s, 2H), 5.85 (s, 1H), 7.00-7.40 (br s, 6H), 7.51 (s, 1H). Anal. Calcd for $C_{19}H_{23}FN_2$: C, 76.52; H, 7.71; N, 9.39. Found: C, 76.48; H, 7.78; N, 9.47. The corresponding (Z) isomer: ^{1}H Nmr : 1.55-1.65 (m, 6H), 1.80 (s, 3H), 2.20-2.50 (m, 4H), 5.05 (s, 2H), 5.81 (s, 1H), 7.00-7.35 (br s, 6H), 7.50 (s, 1H).

1e: from the corresponding imine mixture (0.39 g, 1.3 mmol), K_2CO_3 (0.80 g, 5.8 mmol), TosMIC (0.34 g, 1.6 mmol) in MeOH (8 ml), a 7:3 E : Z isomeric mixture of imidazoles (0.29 g, 66% yield) was obtained, which was separated by column chromatography on silica gel using a mixture 2:1 hexane:AcOEt

saturated with ammoniun hydroxide (28% aqueous solution). **1e**: Ir (ν, cm^{-1}) : 2920, 2850, 1450, 1390, 1350, 1230, 1220, 1165, 1120, 1030, 925; ^1H nmr : 1.78 (s, 3H), 1.80 (s, 3H), 2.30 (m, 4H), 5.05 (s, 2H), 5.60 (br s, 1H), 5.82 (br s, 1H), 6.90-7.35 (br s, 6H), 7.51 (s, 1H). Anal. Calcd for $C_{19}H_{21}F_3N_2$: C, 68.28; H, 6.28; N, 8.37. Found: C, 68.36; H, 6.57; N, 8.32. The corresponding (Z) isomer: ^1H Nmr : 1.70 (s, 3H), 1.72 (s, 3H), 2.30 (m, 4H), 5.05 (s, 2H), 5.60 (br s, 1H), 5.82 (br s, 1H), 6.90-7.35 (br s, 6H), 7.50 (s, 1H).

ACKNOWLEDGEMENTS

Financial support from CAICYT (Grant 84-0087) and CSIC (Grant 163-85) is acknowledged. The authors wish to thank Dr. Patrick Porcheron and Mrs. Madeleine Morinière (Univ. Pierre et Marie Curie, Paris) for supply of β-ecdysone antibody and continuous advise in the performing of EIA assays, and Dr. P. Pradelles (CEA, CEN, Saclay) for a generous gift of the corresponding enzymatic tracer.

REFERENCES

1. G.B. Staal, Ann. Rev. Entomol., 1986, **31**, 391.
2. A. Burger, F. Colobert, C. Hetru, and B. Luu, Tetrahedron, 1988, **44**, 1141.
3. E. Kuwano, R. Takeya, and M. Eto, Agric. Biol. Chem., 1985, **49**, 483.
4. E. Kuwano and M. Eto, Agric. Biol. Chem., 1986, **50**, 2919.
5. S. Asano, E. Kuwano, and M. Eto, J. Pest. Sci., 1984, **9**, 503.
6. E. Kuwano, R. Takeya, and M. Eto, Agric. Biol. Chem., 1983, **47**, 921.
7. E. Kuwano, personal communication.
8. F. Camps, F.J. Sanchez, and A. Messeguer, Tetrahedron, 1988, **44**, 5161.
9. F. Camps, F.J. Sanchez, and A. Messeguer, Synthesis, 1988, 823.
10. F. Camps, R. Canela, J. Coll, A. Messeguer, and A. Roca, Tetrahedron, 1978, **34**, 3067.
11. A.M. van Leusen, J. Wildeman, and O.H. Oldenziel, J. Org. Chem., 1977, **42**, 1153.
12. Y. Bessiere, D.N. Hue-Savary, and M. Schlosser, Helv. Chim. Acta, 1977, **60**, 1739.
13. K. Kadono-Okuda, E. Kuwano, M. Eto, and O. Yamashita, App. Ent. Zool., 1987, **22**, 370.
14. P. Porcheron, M. Morinière, J. Grassi, and P. Pradelles, Insect Biochem., 1989, **19**, 117.
15 E.J. Corey and G. Schmidt, Tetrahedron Lett., 1979, 399.
16 A. Roca, Ph. D. Thesis. University of Barcelona, 1979.

Received, 24th July, 1989